HISTORY OF GENERIC AND SPECIFIC NAMES OF THE MALARIAL PARASITES OF MAN.

THESIS

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[illegible] can be traced directly and indirectly from medical writings from ancient times to the present.

In the fifth century B. C. Hippocrates gave a clear description of these fevers. Celcius in the first century A. D. distinguished the pernicious form of malaria. Many theories were formulated trying to explain the etiology of malarial fevers. The close relation between swamps and malaria yield to the miasmatic theory: organic and inorganic substances found in the air of the marshy districts. Lancisi was the first observer who definitely declared his belief that invisible organisms were the cause of the malaria.

Mitchell in 1849 suggested that certain [illegible] ores occurring in marshy districts might be the etiological factor.

[illegible] founded their discovery of the relation between [illegible],

a bacillus found in the water and soil of malarious regions. The discovery of the infectious agent of malarial fever is due to the French physician Laveran in 1880. In a report to the Societe des Hopitaux he described certain parasites occuring in the blood of malarial patients which he considered to be the cause of the disease. In a posterior monography 1881, he suggested the name "oscillaria malariae" for this newly discovered parasite. Later on the same author describes pigmented spherical bodies of different sizes which possesses amoeboid movements and accepted the term Hematozoon used by Osler.

The discovery of the new parasite arose the interests of several investigators and very soon its principal characters were known. Many names have been suggested for the malaria parasite. The following are the more important steps in the classification.

Machiafana and Celli 1885 laid particular stress upon the smaller forms of the parasite and proposed for these small bodies the term "Plasmodia".

Golgi 1885-1886 discovered the varieties of the parasite belonging respectively to quartan

and tertian fever. Osler 1887 suggested the name Hematomonas specie Hematomona malariae and describes the parasite: globular and spherical bodies, without differentiation of protoplasm containing pigment: different numbers of flagella. Metchinicoff 1887 - places the parasite in the class sporozoa and believes that the organism should be considered among the coccidia and proposes the name "Hematophyllum malariae". Danilewsky 1890 - ranks the parasite among sporozoa and proposes a new group "Haemosporidia". Grassi and Feletti 1890 - placed the malarial parasite among the Rhizopoda and proposed five distinct varieties.

Haemaoeba praecox - quotidian fever
" immaculata - without pigment
" vivax - certain fever
" malariae - quartan fever
Laverania malariae - irregular fevers

Antolisei and Angelini 1890 referred to aestivo anturnal parasite as "Hematozoon falciforme". Danilewsky 1891 - proposed to change the name Haemamoeba by that of cytamoeba.

Marchiafava and Bignami 1891 believed

that they could separate two distinct varieties of the aestivo-autumnal parasite, quotidian and malignant tertian. Welch 1897 - proposed the name Haematozoon falciparum for aestino autumnal parasite. "The name Haematozoon falciforme is objectionable, as it implies that the shape is always falciform. The adjective "falciparum" on the other hand, indicates that the property of forming crescents is a distinctive character of the organism . . ."

Celli and Sanfelice distinguished three genera among the Haemosporidia, Hemogregarina (reptiles), Haemoproteus (birds), and Plasimodium (man). Mannaberg separated three varieties of aestino autumnal parasites, malignant tertian, pigmented quotidian and unpigmented quotidian.

Meyer and Riedes 1907 - deserved Plasmodium immaculation S. Laverania malariae.

Craig 1909 - divided the p. falciparum in two sub-species, - malignant tertian and pigmented quotidian.

Emin 1914 - reported plasmodium vivax variety minuta in the Red Sea Islands.

Stephens 1914 - observed a new species,

plasmodium tenue.

Froilao de Mello 1917 - describes P. tenue in Nove Goe.

Low 1917 - cultivated quotidian parasite (L. Praecox).

Craig 1921 - reported new cases of P. falciparum quotidianum.

Sinton 1922 - reported various cases of P. tenue in India.

GENERA OF MALARIAL PARASITE

Some authors claim that the difference between the parasite of malignant tertian and the other two malarial parasites are characteristic enough to justify the division into two genera. The more important facts adduced are:

In the tertian and quartan parasites all the stages of the asexual cycle occurs in the peripheral blood, whilst in falciparum the segmenting stages take place in the internal circulation. The shape of gametocytes crescentic in falciparum spherical in the other two parasites. The possession by gametocytes of the malignant tertian parasite of a definite limiting membrane or capsule which determines their form. Type of fever regular in tertian and quartan irregular in falciparum. The great majority of authors do not consider that such differences justify the separation of two genera and today the classification of malarial parasite is:

Class	Sporozoa
Sub class	Telasporidia
Order	Haemosporidia
Family	Plasmodidal
Genus	Plasmodium
Species	P. vivax, p. malariae, p. falciparum

IS THERE ONLY ONE OR SEVERAL SPECIES OF MALARIA PARASITES?

Since the beginning we must recognize two main schools with essentially different views concerning the nature of the malarial parasites. The first party is represented by Laveran and his followers, who believed that the malarial parasite was a single polymorphous organism, that there is not constant relation between the different forms in which it appears and the various types of fevers. The second party at the head of which Golgi claims that corresponding to and associated with the main types of malarial fevers we may distinguish different types of the malarial parasite or possible different parasites.

The following are the principal arguments on which is based the theory of unicity of malarial parasites. Laveran 1893 states: "I arrived at the conclusion that the different forms in which the hematozoa of paludism present themselves belong to one and the same polymorphic parasite." "The theory of the plurality of the hematozoa of paludism raises numerous objections. The unity of paludism

from a clinical and anatomico-pathological point of view , is indisputable. Certain forms under certain conditions are often met with e.g. the tertian and the quartan types are much more common in our climate than in hot countries, but it can not be said that here is a home of tertians, there a home of quartans and irregular fevers, it is in the same endemic centers that fevers of different types are contracted and these types vary in a regular manner with the season and the climate. It is a well known fact that the fever often changes in its type in the same patient, the type of fever may even modify itself when patients have left the palustral countries under conditions which exclude the idea of a new infection."

Thiroux supports Laveran's view as to the unity of the malarial parasite. He examined native children in Senegal and found that in the hot weather tropical forms amounted to 96.5 per cent of the whole number examined, and large forms (benign tertian and quartan) to 1.5 per cent, where as in November and December the respective figures of the positive cases were 77.5 and 22.4 per cent, and in March and April they were 64.1 and 35.8 per cent positive cases.

He considered it difficult to admit a summer and winter malaria due to absolutely different species.

Armand-Delille is impressed with the fact that among the French troops in Macedonia the predominant malarial infection between the beginning of July and the end of March following was p. falciparum and the predominant infection from April to July was p. vivax. In October 95 per cent of all cases of malaria were p. falciparum and in July he could find only p. vivax after the month of December p. vivax was completely substituted by p. falciparum. He thinks this alteration of parasites is to be explained in terms of the infecting anophelines. In other words, p. vivax is alone present at the beginning of epidemics, whereas p. falciparum appears in the blood at a time when reinoculations occur, and starting from the moment when the sporozoites are introduced in an almost continuous manner into the blood, the schizonts are very small and garnetocytes assume the form of crescents, well known for their resistant powers. Further, the supposition is advanced that these forms of resistance

and this aspect are the result of a modification of the blood serum, the repeated inoculations of sporozoites favoring the production of antibodies which determine the production of resistant forms of the parasite when anophelines disappear during the winter months or the patient, being in a healthy country, is no longer exposed to their bites, antibodies cease to be produced or are gradually eliminated, and the formation of crescents terminates.

Plehn explains the change of type in malaria infection by the following hypothesis: "The mosquitoes get infected with large parasites (benign tertian) in spring from relapse cases or early primary cases in which the infection has persisted from the previous year. As soon as it is warm enough they transmit the infection to man, who shows the corresponding type of parasite. Later, under the action of summer heat, the parasites in the mosquito assume other characteristics so that they acquire in the first place, the property of destroying the red cells before there is time for the large forms to develop in the latter, and, secondly, that of producing crescents. With those

characteristics, the parasites are transferred to man in the height of summer, and the mosquitoes newly infected by him cause the summer epidemic with the small parasites. In the later relapses, in many cases, the large parasites with rosettes and spherical gametacytes reappear provided the infection has not been stamped out. These later relapses, with large parasites, furnish the material for the next year, thus restarting the cycle." The author suggested that the crescent bodies are not seen in Northern Europe because the temperature is too low to allow them to develop in the mosquitoes.

Grass H. supports the unity of the malarial parasite based on the fact that repatried soldiers from Macedonia have shown first p. falciparum and later on p. vivax and think that mixed infections are the evolution in the change of type also affirms that has been able to see the different steps in the change of type of the parasite, but unfortunately the author does not say which ones these changes are. Grassi concludes that malaria parasites are pleomorphic and poliganetic in the same way as other organisms. Phenomena are encountered, especially in Oenothera lamarkiana and in protozoa, which

might be compared with those met with in the malarial parasites of man. The polimorphism of the malarial parasite must be attributed to a phenomenon of hybridism. However, it is possible that a deeper study undertaken from a new point of view may lead to discover a succession of tertian and crescent forms in accordance with Mendel's law. Pure forms in passing through the body of the anopheles reproduce pure forms and mixed forms reproduce mixed forms whether the gametes be of the tertian or subtertian type. It has been demonstrated by Hegner (1918) on Arcella dentata that the descendents of a single member can become separated into a number of strains which differ from each other as regards their hereditary characteristics. The author concludes that Laveran's theory is being revived today under new and very propitious signs.

Weichman treated 24 cases of tropical malaria for four to five months in a German military hospital in Turkey and found his cases harbored p. vivax at the end of the treatment. He states that recent infection was out of the question and rejects all of the usual explanations - insufficient prophylaxis, quinine fast parasites, low resistance of the patients and insufficient treatment.

On the other side the partisans of the plurality of malarial parasites claim that the supporters of unity have interpreted erroneously some of the facts and that those facts can be better explained on the basis of plurality.

In 1889, Gualdi and Antolisei injected two patients with blood from a patient suffering with a quartan fever and possessing quartan parasites. In each of the inoculated individuals, irregular fevers with aestivo-autumnal parasites developed. These two cases have been adduced as a main support of the doctrine of mutability of the varieties of the parasite, but it was subsequently determined that the patient from whom the blood was obtained had previously suffered from irregular fever, and he subsequently developed characteristic aestivo-autumnal organism.

Von Heinrich giving statistics of 1029 cases treated during seven months, at Sarajevo, records 150 mixed infections. These, in most cases, were not diagnosed until the latent benign tertian parasites appeared in the spring, which is their optimun period of development, just as autumn is the optimun period for the tropical parasite. The two parasites can be coexistent, each has its own characters, no transitional

forms were seen.

Fisher Georg argues that cases of benign tertian occurring in persons who have suffered the previous summer from tropical malaria only, are readily explained when it is remembered that the former infection frequently remains latent for long periods. Quinine prophylaxis is able to keep benign tertian in subjection but often fails to suppress infection with p. falciparum. Hence in cases of double infection, the latter is first in evidence while the former only appears at a later date. He notes that in Macedonia infection with tropical malaria was acquired late in the summer at a time when quinine prophysaxis had become slack and irregular. The author advances the hypothesis that a tropical infection may actually prevent the development of a benign tertian infection.

Seyferth, discussing the seasonal appearance of the types of malaria fever, concludes that the existence of three well defined species cannot be denied, but that under certain conditions, principally climatic, the occurence of types of transitions is observed. As an argument against mixed infections the author cites 280 cases of subtertian in which evidence of mixed infection was carefully

sought i the autumn and winter but none found. However, in the following Spring these relapsed with the presence of tertian parasites. When various pronocatine measures were applied to crescent carriers, tertian parasites were produced.

Worner cites some facts in favor of the distinctness of the tertian and subtertian parasites. It was observed that among the troops of which he was in charge the period of tertian infectio lasted from the end of July to mid - October, and that of subtertian from mid-July to the beginning of December. Blood examinations in all cases were carefully made through the malarial seasons. His conclusions are as follows: Many patients who suffered an attack of tertian in the Spring had had in the previous year first tertian and then subtertian; many patients had had clinically and microscopically only subtertian. All of these men had been in the malaria region during the period when tertian predominated. In the instance of the men who were removed into the district between October and early December and suffered from subtertian, tertian fever in the Spring was never observed. The author concludes that the two types of parasites, P. vivax and P. falciparum, are quite

district.

Leger states that in French Guyana the proportion of infections by the tertian parasite diminish with the age, while the infections by malignant parasite increase in proportion exactly inverses and notes that infections by quartan parasite remain unchanged.

Simons opposes the unitarian theory both on the theoretical ground and from a consideration of the cultural studies. Further, he deals with the question of the influence of temperature on the malarial parasite, a point on which those who hold the unitarian theory lay stress and cites the work of Lacharoff, who fed a leech on blood containing P. falciparum, kept it on ice for four days, injected the blood into himself intravenously and suffered from a tropical pernicious attack. Simons does not regard this experiment as conclusive evidence, but advances it as an argument against the views that variations in temperature can exercise a profound influence on the form of the plasmodium. He also points out that the unitarian theory, which is concerned with a morphological question, depends chiefly on epidemiological and clinical proofs, not on morphological findings. The evidence he obtained from

mixed infections [illegible] the unitarian theory, and he states that in such cases faulty staining technique may lead to fallacious conclusions.

Mayne notes that if one carefully analyzes the accounts in the literature ofapproximately 100 mosquito inoculations experiments an incontrovertible fact presents itself. In every instance of positive result the type of parasite imbibed with the blood of the donor was always reproduced with regularity in the volunter host.

In the positive inoculation experiments performed in the Public Health Service malaria laboratory located in Memphis, Tenn. the evidence presented has been uniformly conformatory of the idea of constancy of species. The author cites the examples of a family in which under the same conditions some of its members show infection by p. falciparum and other p. vivax. After repeated microscopical blood examinations p. vivax was found in two members that harbored p. falciparum and gives as explanation double infection. The author's conclusions are that at any rate unless more data are contributed through blood cultural studies and mosquito inoculation experiments, the principle of transmutation remain merely an interesting

hypothesis [illegible] the tropical states.

The fact that not all the anopheles mosquitoes are capable of conveying all the malarial parasites can only be explained on basis of the plurality of species. Dr. Leran shows that a definite species of anopheles can be the host of a certain type of malaria while other types of malaria cannot develop within it. A. quadrimaculatus becomes infected with the parasites of tertian and quartan but not aestivo-autumnal fever. He found that the distribution of A. crucians about the city of New Orleans corresponds very closely with the distribution of the cases of aestivo autumnal fever. In Formosa Kinoshita found that the epidemic of malaria trouble depends upon the increase and decrease of A. listoni he states further that A. listoni does not occur in Japan so that the country has always been free from pernicious malaria in spite of the fact that persons suffering with pernicious malaria frequently come to Japan. The [illegible] relations of malarial parasites [illegible] favor of the theory of plurality. [illegible] of A. [illegible] - [illegible] the [illegible] [illegible]

[illegible], monkeys and goats with blood containing the plasmodia of human malaria. His conclusions regarding his work with P. vivax are as follows:

From the cases recorded it would appear that the successive inoculations of monkeys or goats with blood containing P. vivax gives raise in those animals to an antitoxin which, when injected in adequated dosage into human beings may be followed by disappearance of the parasites from the circulation and disappearance of the symptoms of malaria. This agent has not apparent influence on infection caused by a variety of the malarial parasite other than that from which it was developed.

The results of the cultivation of the malarial parasite are in favor of the theory of plurality of species. Some of the persons who have been able to cultivate the parasite had observed the change from one species into a different one. Under unfavorable conditions the parasite died without taking the crescent form which accords with some of the partisans of the unicity in the form of resistance.

In the present state of our knowledge

of malarial [illegible] considered [illegible] species or varieties while others think they are only atypical forms.

Stephens 1914 described from a single slide sent from India what he thought was a new malarial parasite with scanty cytoplasm and extreme amoeboid movement. Balfour and Kenyon concluded that the parasites were probably amoeboid forms of P. falciparum, and stated that they not infrequently occur shortly before death.

Craig states that Plasmodium tenue is an atypical form of P. vivax.

Dinton 1915 found four cases of malaria due to P. tenue and expresses the opinion that this parasite is the same P. immaculata. (Meyer- Leader).

In the earliest stages the parasites were very small, round or slightly ovoid forms very like the small "signet ring" forms found in P. falciparum. In stages of medium size oval and bailoi forms and banded forms similar to P. malariae.

segmenting forms of P. vivax [illegible] very regular manner. Crescentic forms resemble crescentic in shape as in P. falciparum.

Discussing the opinion that the tenue form is common shortly before dead the author says that the disease was of a chronic nature in spite of the heavy parasitic infection and even although the patient did not receive quinine, there was a diminution of the number of parasites.

The presence of presegmenting and segmenting forms and of ringed parasites from the Peripheral blood and at the same time the crescentic gametocytes discard the theory of an atypical P. vivax.

P. F. Craig cites cases in which in addition to forms similar to those described by Stephens, there were present also atypical parasites at a late stage of development and concludes that they are digenerative forms, which occur in successive attacks of fever over a long period. According with Basieux and Quintinel the rings of P. vivax often assume a P. tenue form two hours after an intravenous injection of [illegible] gm. of quinine.

Laveran and [illegible] described cases of double infection due to plasmodium vivax in which they observed a tertian and explain that a quotidian form was due to asexual reproduction by simple and multiple fission.

Craig divides the aestivo autumnal parasite into a. falciparum and b. falciparum quotidianum and places the discussion on morphological and clinical differences and concludes that the morphological differences between plasmodium falciparum and P. falciparum quotidianum are as constant and distinctive as those between P. vivax and P. malariae. The quotidian plasmodium causes a simple intermittent quotidian curve, indistinguishable from that observed in a double infection with the benignant tertian plasmodium, while the tertian aestivo autumnal plasmodium causes a typical temperature curve which differs from that observed in any other type of malarial infection. Craig claims that the variation on the type of fevers in the two cases of Darling was due to the administration of quinine.

Darling affirms that P. falciparum possesses inherently both tertian and quotidian tendencies and explains the quotidian curves in quotidian aestivo

[illegible] at [illegible] -tinctly [illegible] forms. [illegible] that. Which [illegible] ex[illegible] r, [illegible] of [illegible] morphological differences [illegible] of [illegible] value on account of the inherent difficulties in differentiating some material [illegible] microscopic examination.

Ross shows pictures of the quotidian parasite (Laverania praecox) whose whole cycle is completed in 24 hours and says the culture shows a marked tendency on the part of the developing parasites to agglutinate in larger or smaller masses. The mature sporulating forms show 8 spores or less, the infected corpuscles are much larger than the normal ones.

Bertarelli described cases of aestivo autumnal fever in which the parasites were reduced to the size of an amoebula, [illegible] small masses of chromatic substance.

Until further study it [illegible] difficult to decide [illegible] differences [illegible] the morphology [illegible] character [illegible] material [illegible] established [illegible] so different varieties [illegible] are atypical forms.

[illegible] ...

[illegible] ... responsible for [illegible] ... to great [illegible] ... controversy is far from being settled. [illegible] ... between [illegible] ... development of these [illegible] ... attempts to explain [illegible] ... questions more or less probable, chief amongst the views advanced by various authority at different times are the following:

1. The parthenogenetic view suggested by Grassi and mainly associated with the name of Schaudinn. He pointed out that in an ordinary case of [illegible] ... the sexual form disappeared very soon, and [illegible] ... by the male gametes living the female gametes alone. [illegible] ... difficult to understand how the [illegible] ... substance unless something happened to the female [illegible] ... during the [illegible] ... life. [illegible] ...

[illegible] fore [illegible] d from t[illegible] [illegible] l form [illegible] man [illegible] by [illegible] of [illegible].

The critical [illegible] in th[illegible] of th[illegible] ev[illegible] made by J. Thomas is concluded that [illegible] in the first place misinterpreted [illegible] of schizonts [illegible] gametocytes as indicating schizo[illegible] of the macrogametes, [illegible], that he [illegible] induced as early stages in the development, nuclear changes which occur normally in maturation.

2. The schizogony goes on without intermission through the intervals between relapses. By a process of natural selection schizogony is kept up but the numbers [illegible] survive at any [illegible] time are too small to produce symptoms or to be found in the peripheral blood, when the special conditions are removed a relapse occurs as pointed out by [illegible]igami it is not necessary to suppose that such forms as survive differ morphologically from others which perish. The resistance of the [illegible] expressed in terms of antibodies, supplies a parallel explanation in the other cases.

3. The forms surviving [illegible] may [illegible] the blood [illegible]. Nevertheless, it is

[illegible] to [illegible] multi[illegible] enter [illegible] are turned to [illegible]. The [illegible] inoculation [illegible] up of the [illegible] tially [illegible].

4. The [illegible] of sporulated sexual residual forms. These forms if intracorpuscular to begin with, would be capable of living free in the plasma after the disintegration of the red cell. Some workers have described in old parasitically relapsing cases forms which correspond neither to a schizont nor to a gametocyt.

5. The amount of glucose in the blood [illegible] to be a cause of relapses. This hypothesis is based on the fact that malarial [illegible] cannot live with a concentration of 0.5 per cent of glucose. Von [illegible] found that the [illegible] in the blood was found to be within normal limits - [illegible] in tertian, [illegible] in malignant ague, on the average.

[illegible] of sugar
[illegible] the maximum 0.11% to 0.16%.

[illegible]

[illegible] after muscular effort
(child) and fatigue, the proportion of sugar in
the blood may be increased (Dudgeon).

[illegible]

[illegible] following [illegible] of the vivax [illegible] first [illegible] and [illegible] the original parasite in culture. The [illegible] since been repeated by several workers, [illegible] multiplication of the parasites in the culture tube has been observed in the case of all the [illegible] successive generations of the malignant tertian parasite.

The course of the asexual development in artificial cultivation is known to be practically identical with that occurring naturally in the human host. The plasmodium grow in a thin layer near the top of the coil sediment, beneath which zone the parasites die. The parasite has been cultivated only in the red cells of human blood and are destroyed by the leukocytes as soon as they are liberated from the erythrocytes, and also by the serum. In the majority of cases it was found that dextrose must be added to the medium in order to obtain growth of the parasites. Time and [illegible] the destruction activities of the leucocytes centrifuged the defibrinated blood until there were few, if any, red cells above, the [illegible] [illegible] [illegible] at the bottom.

[illegible] cotton [illegible] inches. [illegible] blood co[illegible] [illegible] are then drawn up from the deeper part of the corpuscular layer. The most favorable temperature found for the cultivation of these protozoa is about 40° C. Two or three generations of parasites grow in such cultures, then the plasmodia begin to die out so that if the culture is to be perpetuated, they must be transplanted to freshly prepared blood corpuscle cultures of the same kind.

Thomson was able to observe the growth of the parasite and affirms that is unnecessary to destroy the complement or to remove the leucocytes, growth moreover takes place through the whole thickness of the corpuscles and not only on the superficial layer. The time required to complete development varies from twenty-five to fifty hours.

Now devised a method of cultivation less elaborate and that requires less amount of blood.

The apparatus used by the author consists of an ordinary potato culture tube, a small culture tube with a flat bottom in order to have a thin layer of red cells. For the seclusion of the anaerobic conditions necessary for the growth of the organisms, pyrogallic acid is used. The author succeeds

in cultivating the quartan, benign tertian, malignant tertian or falciparum, and the quotidian parasite (Laverania praecox) which has the whole cycle of 24 hours.

Chamberland used a modification of East's procedure which is as follows:

Instruments required:

1. A 10 cc syringe and needle
2. Test tubes with apparatus for defibrination of the blood
3. Test tubes for inoculation
4. Capillary pipetes.

Media - a 50 percent solution of dextrase doubly sterilized, a 7 percent physiological solution of sodium chloride to each litre of which has been added 0.75 centigrames of sodium citrate.

Freshly drawn blood is centrifugated, the serum and white blood corpuscles are removed by the pipette and the red blood cells alone retained. Warm physiological saline is added then dextrase medium in the proportion of 15 cc for each 5 cc of the original blood.

Results - P. malariae and vivax were found too delicate to accommodate themselves to adverse culture conditions but falciparum can survive

and to through the cycle of development.

Linton uses a tube of special size devised by him that has the following advantages: a large surface of red blood corpuscles with a minimal amount of blood; a maximum depth of serum with a minimal quantity. In an anaemic malarial patient often is very difficult to get from the finger the amount of blood which after defibrination would be sufficient to produce a column of serum at least 12 m.m. high on the top from the layer of red blood cells. This difficulty can be obviated by using ascitic or hydrocele fluid.

The ascitic fluid is drawn off with strict aseptic precautions into sterile flasks. To each 100 cc of the ascitic fluid is added 1/5 cc of a sterile 50% solution of dextrose. The flasks are then heated for half an hour at 56° C. to kill as much complement as possible without interfering with the composition of the fluid.

Optimum temperature - 37° C.

Results - malignant tertian, the growth seemed to go on to the third generation - P. vivax degenerated before sporulation.

The object of provocatives is to bring a relapse or at least to make appear the parasites in the peripheral blood where they can be detected by microscopic examination and ascertain whether malarial patients are permanently cured. The subcutaneous or intramuscular injection of normal serum, milk, iron, salvarsan, ergotin, as well as various plans such as the application of X rays, cold douches, ice, etc., to the abdomen over the splenic area are among the so called provocatives which have been tried with that object.

King H. in 58 cases treated by strichnine reaches the following conclusions:

1. Strichnine in large doses (20 - 30 mgrms) will in 50 % of cases definitely contract a large spleen but will have no appreciable action on small ones.

2. In most cases it will not increase the number of parasites in the peripheral circulation; possibly this action might occur in some of the cases in which marked contraction of a large spleen takes place. As a routine aid to diagnosis, strichnine has no place.

Reports indicate that the injection of

adrenalin gives the most perfect type of positive results.

According to Dazzi the administration of adrenalin (1 milligramme) does not bring a typical malarial attack but is uniformly followed by the discovery of plasmodia in the blood stream. The presence of parasites in the blood is transitory, commencing about 20 minutes after injection, it reaches its height in an hour and after 24 hours parasites are no longer to be found.

The effect of chronically enlarged spleens which contain much fibrous tissue is less marked.

By this measure is [illegible] the regular taking and absorbing of quinine in such a manner as will anticipate the first dose of sporozoites injected by a mosquito. It is, therefore, designed to prevent primary attacks of malaria. Quinine has been used to prevent malarial fevers for quite a while and in late years has been extensively administrated for this purpose. The Italian government has used quinine systematically since 1900.

The results according with the statistics of Celli can not be more encouraging. The average number of deaths per year for the 10 years preceding 1902 in all Italy was 14,046; the number of deaths from malaria in the period 1911 - 1917 was 7,853, - almost one fourth of the former number. The cases of fever from one section has been reduced from 11,053 per year to 2,974 as no other means have been taken to prevent malaria among these people, this reduction must be ascribed to quinine taken as a preventive.

Stephenson - New Guinea - claims that he was able to entirely rid the place of malaria by the use of quinine alone.

Craig at Camp Whitesburg in Santiago the Isthmus, where nearly 30 per cent of the regiment of cavalry entered the hospitals with malaria during the malarial season, when one gram every seventh day and resulted in a diminution of over two thirds in the malarial infection. He points out that "at this post every other prophylactic method was used previous to the use of the quinine".

On the other hand, many investigators have found that quinine has very little if any value as prophylactic in malaria and some of them believe quinine in large doses for long period cause cessation of every energy production and eventually death, and doubt that quinine in harmless doses can act as a reliable prophylactic (J. W. Corwell)

Paoliti says that in Alvania 1917 - 1918 with the rarest exceptions the men treated contracted malaria among the prisoners in the districts of Forte and Maccarese it was found that a dose of 0.40 grms. of quinine was insufficient to prevent fever and often a dose of 1.40 grms. was not enough to arrest it. This fact is attributed to the frequency of new infections due to the great number of infected mosquitoes in their rooms.

Several theories have been expressed trying

to explain the difference of results with quinine as malaria prophylactic -

1. The quality of quinine that in many instances has been adulterated or contains less active alkaloids than supposed.

2. The form in which is administered, pills or tabloids, that are likely to pass through the intestine unchanged.

3. The people really do not take the quinine. In India the English physicians found that the soldiers used to spit out the drug. Now they give quinine in solution and the soldier must recite his regiment's number after taking quinine so as to be sure it has been swallowed. By this method the number of cases has reduced considerably.

4. The effectivity of quinine varies with the different species of malaria parasite. "Malarial" fevers are usually regarded as a single entity, and not as three distinct fevers due to three different species of parasites and of which are not equally affected by quinine". (Actor [illegible].) Recent experiments show that quinine is specific for malignant tertian parasite as the cure rate is 90% or over, whilst for benign tertian the cure rate with each course of treatment is only about 55%.

The authors differ on the dose of quinine to be given as a preventive of malaria. There are two principal methods of administration, - the one canonized by Koch, large doses at considerable intervals; the other, smaller daily doses, as used in Italy. In the first method, 1 grm. (15 grains) are given daily every ninth and tenth day. A Plehn uses 1 grm. once a week. Ziemen advocates one grm. given up ever, fourth day and if quinine be disagreeable in its effects that enquinine in doses of 1 grm. be substituted. He does not believe that in regions where pernicious forms of malaria occur Koch's method is sufficient.

Celli believes in the daily administration of quinine in average doses of 0.4 grms. for the children 0.3 grms of tannate compounded with sweet chocolate.

It has been suggested that the amount of quinine that prevents against malaria varies in each locality, according not only with the type of parasite but also is in relation with the infection, - the heavier the infection, the larger the quantity of quinine required, - and in consequence that a quinine index must be worked out to know the amount of quinine required in each locality.

Today we [illegible] to recognize that the use of quinine as a prophylactic lowers the malarial sick rate and that it, at some times, fails materially to diminish the incidence of malaria in very badly affected countries, it lessens the severity of the disease and, in consequence, mortality.

Its use is specially adapted in farming community where it is not practicable economically to get rid of malarial mosquitoes.

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STUDIES ON THE MALARIAL PARASITES OF MAN

by

Dr. C. Abadie.

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